Docket No. 10806-151

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Karen E Mavis



**PATENT**



**IN THE UNITED STATES PATENT & TRADEMARK OFFICE**

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| Applicant: | Andreas CASTAN | : | Paper No.: | |
| Serial No.: | 09/732,638 | : | Group Art Unit: | 1655 |
| Filed: | December 8, 2000 | : | Examiner: | B. Sisson |

For: **Production of Peptides**

B/8
1217
10/8/01

## AMENDMENT

Box Fee Amendment
Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Official Action dated June 22, 2001, please amend the present application as follows:

**In the Claims:**

Please amend claims 1, 5, 11 and 12 to read as follows:

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B1

1. (Twice Amended) Method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period.

B2

5. (Twice Amended) Method according to claim 1, wherein the oscillation feed has a sinus pattern.

11. (Amended) Method according to claim 2, wherein the oscillation feed has a sinus wave pattern.

B8

12. (Amended) Method according to claim 3, wherein the oscillation feed has a sinus wave pattern.

Please add the following claims 21-27:

--21. (NEW) Method according to claim 1, wherein the cultivation is carried out under aerobic conditions.--

--22. (NEW) Method according to claim 1, wherein the oscillation feed has a square wave function of +/- 30% of standard and a wave period of 1 minute.--

Sub C2 7

--23. (NEW) Method according to claim 1, wherein the oscillation feed has a wave amplitude of from about +/- 5% to +/- 60% of standard and a wave period of from 1 minute to 30 minutes.--

B9

--24. (NEW) Method according to claim 1, wherein the oscillation variation in stirring speed is +/- 20% of standard with a square wave period of 1 minute.--

--25. (NEW) Method according to claim 22, wherein the oscillation variation in stirring speed is +/- 20% of standard with a square wave period of 1 minute.--

--26. (NEW) Method according to claim 1, wherein the microorganism is *E. coli* and wherein the recombinant peptide is human growth hormone.--

--27. (NEW) Method according to claim 1, wherein the recombinant peptide comprises recombinant human growth hormone, immune interferon, tissue plasminogen activator, or human insulin.--

## REMARKS

The Official Action dated June 22, 2001 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration and an early allowance are requested.

By the present Amendment, claim 1 is amended for a matter of form and to recite that the method is conducted without exhaustion of the organic carbon source during the oscillation period in accordance with the teachings of the specification at page 5. Claims 5, 11 and 12 are also amended for matters of form. A Version With Markings Showing Changes Made is attached. Claims 21-27 are added. Support for claim 21 may be found at page 5, lines 7-8, support for claims 22-25 may be found at page 5, lines 16-21 and in Figs. 1 and 2, support for claim 26 may be found in original claims 3 and 7, and support for claim 27 may be found at page 1, lines 14-19. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 1-20 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification does not reasonably provide enablement for use of any organic carbon source, the recombinant production of any protein, or the use of any type of cell. The Examiner acknowledged that the specification is enabling for the method of claim 1 wherein the recombinant human growth hormone is produced in *E. coli*, the carbon source is not exhausted, the culture conditions remain aerobic, the feed stock is added as a square wave function of +/- 30% where the wave period is for one minute, and the feed stock is added during agitation of +/- 2-% with a square wave period of 1 minute.

This rejection is traversed on the basis that the present claims are fully enabled by the specification in accordance with the requirements of 35 U.S.C. §112, first paragraph, and reconsideration is respectfully requested.

More particularly, claim 1 recites a method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period. As the Examiner notes at page 4 of the application, the relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry. Such an artisan will easily recognize that the method for the production of recombinant peptide as disclosed and claimed may be used with various organisms expressing different recombinant proteins, without undue experimentation. That is, methods for the production of recombinant peptides by fed-batch cultivation of a microorganism in a bioreactor are well known in the art and the present specification enables one of ordinary skill in the art to conduct the known cultivation, with the inventive addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period, without undue experimentation.

Specific and enabling details of the cultivation as claimed are set forth at page 5. Additionally, the present specification clearly discloses methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor as recited in claim 1 at, for example, page 1, lines 6-10. As set forth at page 5, lines 16-23, both the period time for the oscillation curves and the amplitude for the oscillation curves can be determined by a person skilled in the art for each protein, type of cultivation, medium and the like. Finally, while the specification discloses at page 5, line 12, that aerobic conditions should be maintained, one of ordinary skill in the art will appreciate that this disclosure is relevant to the specific embodiment of glucose as referenced at page 5, line 8 and not to the general disclosure of the production methods.

As a matter of Patent Office practice, a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support, *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971) (emphasis by court). In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement, *Id.*, at 370 (emphasis by court). The present specification provides a teaching of the manner and process of making and using the inventive production method in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented. Moreover, other than broadly stating that the claimed invention relates directly to "matters of physiology and chemistry" which require "greater levels of enablement," Applicant finds no specific evidence or reasoning by the Examiner which is inconsistent with the statements set forth in the present specification. Thus, the present specification must be taken as enabling for the method for the production of recombinant peptide as defined by claims 1-20.

It is therefore submitted that the rejection under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 1-4 and 8-10 were rejected under 35 U.S.C. §102(b) as being anticipated by Yang, "Optimization of a Cultivation Process for Recombinant Protein Production by *E. Coli*," *Journal of Biotechnology*, 23(3):271-89 (1992), STN, File Medline, Abstract No. 92304528. The Examiner asserted that Yang discloses the optimization of protein production in fed-batch cultures of *E. coli* where glucose is added to the culture in an incremental manner which meets the limitations of Applicant's square wave pattern.

However, Applicant submits that the methods defined by claims 1-4 and 8-10 are not anticipated by Yang, and are patentably distinguishable therefrom. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

As noted above, claim 1 is directed to a method for the production of recombinant peptide for fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period. Improved peptide quality and/or yield may be obtained.

The Examiner's rejection relies on an abstract of the Yang publication. For the Examiner's convenience, submitted herewith is a complete copy of the Yang publication. A Form PTO-1449 citing the Yang publication is attached and it is requested that the Examiner initial and return the Form PTO-1449 to make the entire Yang publication of record in this application.

Yang discloses a single-stage fed-batch bioprocess for the production of the recombinant protein ß-galactosidase by *E. coli*. In the summary, Yang discloses that an exponential substrate feeding schedule was used to maintain optimum conditions and that inhibition of growth and protein expression caused by excessive concentrations of glucose and acetate was investigated and subsequently minimized with an incremental nutrition feeding schedule which limited the specific growth rate of a culture. Yang appears to teach a method wherein the culture feeding schedule requires glucose to be added exponentially in a step-wise fashion (see page 280, third full paragraph, and page 282, Fig. 6). Additionally, Yang appears to teach that the glucose should be completely assimilated between addition steps (page 280, third full paragraph).

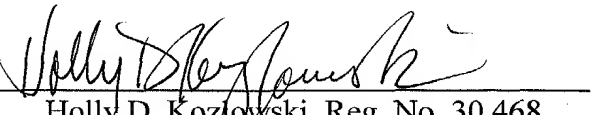
However, Applicant finds no teaching by Yang of a method as defined in claim 1 wherein cultivation is carried out by the addition of the organic carbon source in oscillation

feed and/or by oscillation variation stirring speed, without exhaustion of the organic carbon source during the oscillation period. To the contrary, Yang specifically teaches complete assimilation of glucose between separate addition steps. Additionally, Applicant finds no teaching or suggestion by Yang of an oscillation feed having a square wave pattern or a sinus wave pattern.

Anticipation under 35 U.S.C. §102 requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed Cir. 1986). In view of the failure of Yang to teach a method as defined by claim 1, particularly wherein cultivation is carried out by addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period, Yang does not disclose each element of the claims under consideration and therefore does not anticipate claim 1, or claims 2-4 and 8-10 dependent thereon, under 35 U.S.C. §102. It is therefore submitted that the rejection based on Yang has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§ 102 and 112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

By 

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